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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,612	03/29/2000	SERGIO ABRIGNANI	0366.103	7749

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EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	13

DATE MAILED: 03/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,612	ABRIGNANI ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

Claims 1-6 and 8-26 were cancelled, claim 7 was amended, and new claims 27-31 were added in Paper No. 12 submitted November 9, 2001.

Claims 7 and 27-31, drawn to a method for treating an HCV infection, are pending and under examination.

This application is not in complete compliance with the sequence rules. Each sequence that is embedded in the text, the figures, or the claims must be represented in computer readable form and in the paper sequence listing (37 CFR 1.821(d)), and accompanied in the text by an appropriate SEQ ID NO. Figure 1 shows six different amino acid sequences, for human, chimpanzee, green monkey, hamster, rat, and mouse CD81; however, it appears that the sequence for human CD81 has been omitted from the CRF and the paper sequence listing which was submitted February 22, 2001, and the SEQ ID NO. for the human sequence does not appear in the Brief Description of the Drawings on page 13. Applicant is given the same time period in which to comply with the sequence rules as is available to respond to this Office action. Please see the attached Notice to Comply.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite because it recites "a CD81 protein or a functional equivalent thereof" for reasons made of record in the previous Office action.

Applicant has pointed out that the specification at page 2, lines 21-22, defines a functional equivalent of CD81 as "a compound which is capable of binding to HCV, preferably to the E2 protein of HCV."

Applicant's remarks have been considered but not found persuasive; the intended limitations of "functional equivalent" of CD81 remain unclear, even given the definition provided. Many compounds could be "capable of binding to HCV," including, e.g., a polyclonal antiserum from an HCV-infected patient or a monoclonal antibody to HCV core protein, or a lipoprotein, any of which could be interpreted as representing non-preferred embodiments of Applicant's treatment claims. Further, relying upon language such as "preferably" to define a term makes the term inherently unclear since it is not clear whether "preferably binding to the E2 protein of HCV" is to be taken as a limitation or a suggestion.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 27-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for reasons of record in rejecting claim 7 in the previous Office action.

Claims 7 and 27-31 are drawn to the pharmaceutical use of a CD81 or functional equivalent thereof to reduce viral infectivity and encompasses human treatment using the protein or a functional equivalent. The specification does not teach that administration of a CD81 protein or any portion of a CD81 protein, or any compound

that functions in the same way as CD81 insofar as it is capable of binding to HCV, in fact is of any therapeutic value to a human subject in reducing viral infectivity. The instant specification at page 4 speculates that the protein or its functional equivalent may have a therapeutic effect. Rice (Hepatology 29:990-992, 1999, of record) points out that merely blocking or preventing HCV E2-CD81 interaction may or may not be of therapeutic value. (See, e.g., Rice, paragraph bridging pages 990-991). Petracca et al. (Journal of Virology 74(10):4824-4830, 2000, of record) disclose that internalization of ligands by CD81 is rather inefficient and that it appears that certain hepatoma lines bind HCV in the absence of CD81, illustrating that mere knowledge of the association of CD81 and HCV is not sufficient to support predictability in treating HCV infection by administering a CD81 or a functional equivalent thereof. One of skill in the art requires more than speculation and indeed requires some factual evidence that a beneficial effect in the form of reducing viral infectivity is actually obtained by administration to a human of a CD81 protein or a functional equivalent of a CD81. In the absence of any such factual evidence, the specification cannot be said to enable one skilled in the art to use the invention as claimed.

Applicant has reviewed that standards for enablement and has argued that sufficient information has been provided in order to enable one of skill in the art to make and use the invention as claimed. Applicant has cited Example 5, showing the binding of human CD81 to recombinant HCV E2; Example 6, showing that the extracellular loop of CD81 binds recombinant E2 and viral particles; Example 7 and Figure 12, showing that proteins containing the human EC2 loop of CD81 bound to E2 and inhibited binding

of E2 to human cells, and has argued that such in vitro assays are considered "indicative of therapeutic efficacy." Applicant has argued that use of CD81 which binds circulating HCV would eliminate or reduce the ability of the virus to be internalized and the ability of the virus to replicate. Applicant has pointed out that the level of skill in the art is "remarkably high" and that no methodologies are required in order to practice the invention that extend beyond the ability of the routineer.

Applicant's arguments have been considered but not found persuasive. The unpredictability of the art is appropriately taken into consideration, as is the extent of the disclosure. The examples cited are not commensurate in scope with the claims, and there is no basis for extrapolating from these *in vitro* results to a reasonable expectation for a successful treatment for human HCV infection, although that is clearly the intent of the claimed methods. It is not apparent that even the binding of a CD81 protein to HCV *in vitro* could be extrapolated to the same capacity to bind HCV *in vivo*, since, for example, HCV in an infected individual is likely to be complexed with antibodies and/or lipoproteins, and it is not known to what extent the existence of these complexes would be likely to affect the binding of CD81 to HCV. Further, HCV E2 comprises a hypervariable region, and it is not apparent that all variant HCV E2's would be expected to retain the capability to bind a CD81 protein. Still further, since the "functional equivalent" as claimed could be a small molecule bound to HCV E2, and since CD81 is unlikely to be the sole HCV receptor (Rice, cited above), there is no disclosed basis for expecting that a small molecule bound to HCV E2 would interfere with infectivity via a different HCV receptor.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:30-5:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
March 20, 2002

1.

Application No.: 09/509612

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: missing Sequence) See Fig 1

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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